1 Endoscopic Lesion Recognition and Advanced Imaging Modalities

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Introduction

The field of gastrointestinal endoscopy has evolved in the last 50 years as a consequence of significant advances in engineering, physics, chemistry, and molecular biology among others. One of the most important goals of endoscopy is in detecting and characterizing premalignant or early neoplastic lesions that may be suitable for curative therapies. The explosive growth of optical, cross-sectional, and molecular methods allows us to recognize subtle lesions that may have been missed, in addition to predicting histology and guiding endoscopic therapy.

The development of fiber-optic technology was a determinant step that permitted the introduction of flexible gastrointestinal endoscopes in 1957, which replaced the old, rigid, and semiflexible endoscopes [1]. Conventional video endoscopy was then developed in 1993 by using charge-coupled devices (CCDs), which enabled visualization of real-time imaging on a monitor [2]. During the last decade, developments in video endoscopy resolution and monitor definition have led to the introduction of high-definition white light endoscopy (HDWLE), which is now considered as the standard of care [3].

Despite these tremendous advancements in video endoscopy, subtle lesions can still be missed. Thus, other optical, cross-sectional, and molecular methods have rapidly evolved as an adjunct to HDWLE. Optical technologies such as conventional and virtual chromoendoscopy have been available in clinical practice for several years. In contrast, cross-sectional methods with the ability to provide real-time histology images such as confocal laser endomicroscopy (CLE), optical coherence tomography (OCT), and volumetric laser endomicroscopy (VLE) are still being evaluated, not yet available to most endoscopists, and hence not ready for routine clinical use. Most recently, molecular imaging has emerged to detect specific targets and guide individualized treatments, but it is at early stages and only available for research purposes. In this chapter, we will review each of these advanced imaging modalities (AIMs) and their applicability in recognizing different gastrointestinal lesions in clinical practice.

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Table 1.1 Pros and cons of different advanced imaging modalities

Advanced imaging modality	Pros	Cons
Conventional chromoendoscopy	Detailed surface pit pattern Useful for dysplasia detection in IBD	Adds time and cost (dyes) Potential risks with vital stains Lack of validated classification systems Evaluation limited to the mucosa
Virtual chromoendoscopy	Detailed surface pit and vascular pattern Easy and cheap on/off button Validated classification systems Useful for neoplasia detection in Barrett's esophagus, stomach lesions, and colon polyps Useful for colon polyp characterization	Evaluation limited to the mucosa Interpretation requires training
Autofluorescence imaging (AFI)	Imaging at greater depth	Low specificity, high false positive rates Low resolution Requires special equipment
Confocal laser endomicroscopy (CLE)	High resolution Visualization of mucosa at cellular level, allows in vivo histology	Time consuming, costly Typically requires probes (pCLE) Requires IV contrast agents Evaluation limited to the mucosa
Optical coherence tomography (OCT)/ volumetric laser endomicroscopy (VLE)	Visualization of mucosa and submucosa at cellular level VLE can mark abnormal area	Low resolution Requires special equipment, costly Requires training
Molecular imaging	High specificity	Adds time and cost Requires special equipment Not available for routine clinical use

Description of Technologies

Table 1.1 summarizes the pros and cons related to the use of each advanced imaging technology in clinical practice.

White Light Endoscopy (WLE): Standard vs. High Definition

Equipment required for video endoscopy includes a video processor, a light source, the endoscope, and a monitor. An external xenon light source provides the full spectrum of visible white light which travels through fiber-optic glass bundles and is emitted through a lens at the end of the endoscope [4]. Light is reflected off the mucosa, through the objective lens of the endoscope, and reaches the photosensitive surface of the CCD – a small chip in the endoscope tip that senses an image. The CCD captures the image and transmits the charge through electrical wires to the video processor, where a digital image is produced. The initial standard-definition (SD) endoscopes were equipped with 410,000 pixel CCD that provided a digital image that was 640 (width) by 480 (height) [5]. Soon after came the realization that image quality was largely dependent on resolution, which is a function of CCD pixel density.

HDWLE uses smaller chips that produce images with a resolution of more than a million pixels and that are displayed in monitors with either 4:3 or 5:4 aspect ratios and at least 650 pixels in height [6]. In order to truly capture HD images, all of the endoscopy equipment must be HD compatible (endoscope, CCD, processor, monitor, and transmission cables). HD monitors can display progressive images where lines are scanned consecutively and the images painted 60 times per second, which produces fewer artifacts for moving objects. Optical magnification with HD endoscopy can provide images up to 150 times the original size with preserved resolution. This function can be activated with a button in newer endoscopes through a system called near focus, which modifies a mechanical movable lens at the tip of the endoscope [7].

Conventional Chromoendoscopy

This type of AIM enhances the GI mucosa with topically applied dyes to outline lesion borders, highlight surface changes, and delineate mucosal depth. Several methods of dye application are employed depending on the target surface area. For focal suspicious lesions, a 60 mL syringe of diluted dye can be pushed through the instrument channel of the endoscope, and the target area is then examined closely. In cases targeting a larger area of tissue, such as patients with inflammatory bowel disease, a more efficient method for delivering dye is through the water jet irrigation system after mixing 250 mL of normal saline with dye in various concentrations [8]. Each dye has distinct chemical properties designed for different clinical applications.

Methylene blue is a vital dye that is absorbed by the epithelial cells of the small intestine (e.g., intestinal metaplasia, IM) and colonic crypts. Absorption generally occurs within 1 minute of topical application, and the effect remains for up to 20 minutes. Whereas "normal" mucosa will soak up the dye color, neoplastic or inflamed mucosa will absorb little or no dye. Thus, a brighter and unstained area is a clue for pathology. Lugol's solution is another vital dye used mostly for screening of esophageal squamous cell cancer in high-risk populations. Suspicious areas more likely to harbor high-grade intraepithelial neoplasia appear as well-demarcated unstained regions of >5 mm, often termed the "pink color sign" as these areas retain a pink mucosal hue in contrast to the iodine-stained surrounding mucosa (Fig. 1.1) [9]. Other but less used vital dyes include crystal violet and cresyl violet.

Non-vital dyes are applied to the surface and provide contrast but without being absorbed by the epithelial cells. Indigo carmine is one of the most commonly used non-vital dyes. It collects in the pits and grooves of the mucosa, thereby enhancing visualization of mucosal structures, surface topography, lesion depth, and borders. Acetic acid is a weak acid that induces a chemical reaction in the mucosa with a goal of delineating epithelial structures. Endoscopic delivery of acetic acid through a spray catheter temporarily alters the structure of surface epithelial glycoproteins, which lasts for 2–3 minutes [10]. The unbuffered acid facilitates disruption of disulfide and hydrogen bonds, provokes deacetylation, and in turn denatures the proteins. Repeat application of acetic acid may be necessary to sustain the effect.

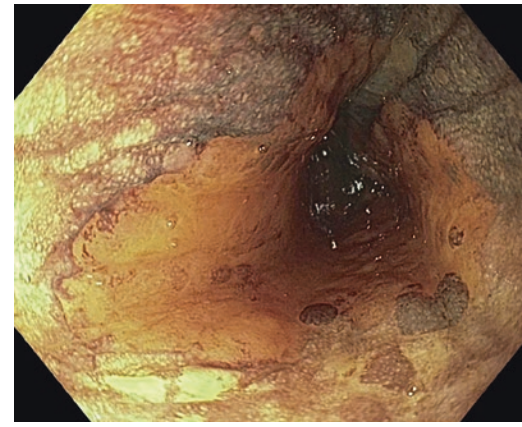

Fig. 1.1 Squamous cell dysplasia with chromoendoscopy using Lugol's solution (unstained areas representing areas of dysplasia)

Virtual Chromoendoscopy

Virtual chromoendoscopy uses optical lenses and digital processing programs to achieve similar results as conventional chromoendoscopy but with the ease of only pressing a button. The most widely used of these systems is narrow band imaging (NBI, Olympus), which is based on the optical phenomenon that the depth of light penetration into tissue depends on the wavelength; the shorter the wavelength, the more superficial the penetration. In WLE, light at wavelengths 400–700 nm illuminates the surface mucosa and reproduces all images in their natural color. NBI applies an optical filter in real time using a red-green-blue illumination system at a narrower range of 400–540 nm designed to match hemoglobin absorption [11]. This allows structures with high hemoglobin content to appear dark (surface capillaries, brown; submucosal vessels, cyan) which provides a contrast to the surrounding mucosa that reflects the light.

Other systems use the full spectrum of white light to capture images and then perform post-imaging processing. The Fujinon Intelligent Chromoendoscopy (FICE) (Fujinon Inc., Japan) system applies software-based technology to modify images captured through the standard endoscopic video processor [12]. The algorithm selectively enhances specific light wavelengths and creates a reconstructed FICE image. A similar technology is iScan (Pentax, Japan), which uses a digital post-processing system to reconstitute an image [13]. The endoscopist can switch between surface, color, or tone enhancement modes by pressing a button to improve visualization of specific features. Another modality is called blue laser imaging (BLI) or Lasero (Fujinon), which uses a two-laser system. BLI was created in response to the limitations of FICE and NBI as a way to combine the strengths of each individual technology [14]. The limited-wavelength blue laser highlights the mucosal vasculature (similar to NBI), while the second laser induces fluorescent light to illuminate the target.

Autofluorescence Imaging (AFI)

This is a technology dependent on endogenous fluorophores within the GI mucosa, the most important of which is collagen. Fluorophores are naturally occurring substances that absorb energy from short-wavelength light (blue) and in turn emit longer-wavelength light (fluorescent). The patterns of fluorescence vary based on the metabolic activity, blood flow, and biochemical characteristics of the tissue, which can be abnormal with neoplasia and inflammation. Endoscopes with AFI capability have a rotating filter in front of the light source that delivers narrow-spectrum blue light (390–470 nm) alternating with green light (540–560 nm) [15]. There is an additional interference filter whereby only fluorescent and green light are filtered through the CCD to be processed. In the resulting image, normal tissue appears green, and abnormal mucosa appears dark reddish purple in color.

Confocal Laser Endomicroscopy (CLE)

This technology is based on light microscopy, but requires contrast agents administered intravenously (fluorescein) or topically (fluorescein or acriflavine hydrochloride). A laser is then focused by an objective lens to illuminate a single point in the focal plane. Light reflected back from that focal point will converge through a pinhole to the detector [16]. Light that comes from outside the focal point will be scattered and not collected. When the detector processes the light, a high-resolution image at a gray scale will be created showing cellular structures from the mucosal layer (250 um), but not deeper structures. Confocal imaging can be endoscopy based (eCLE) or probe based (pCLE) [17]. Probes are designed to pass through the endoscope working channel toward the target tissue in the biliary tree, upper GI tract, or lower GI tract.

Optical Coherence Tomography (OCT) and Volumetric Laser Endomicroscopy (VLE)

OCT is a disposable probe-based system where long wavelengths of light are used to penetrate into areas of interest and create cross-sectional images [18]. This is similar to endoscopic ultrasound, but infrared light is used instead of acoustic waves to create high-resolution images. A single light source emits two beams, one that is directed at the target tissue and the other to a reference mirror. Light is reflected from both sources and then combined again at a detector to produce interference, which is measured and translated into an image.

VLE uses technology similar to OCT, where rapid scanning facilitates capture of images at a depth of 3 mm with resolution to 10 mm [19]. It is designed for use within a circumferential lumen such as the esophagus. A balloon is passed through the instrument channel and inflated. Then an optical probe is passed through the balloon. The balloon is rotated 360 degrees as the probe is pulled back slightly. The probe VLE has the potential to quickly and effectively image large areas in short periods of time (the entire 6 cm length of the balloon in 90 seconds).

Molecular Imaging

Molecular imaging is an innovative technology where targeted probes are directed to specific molecules in the GI tract. A molecular probe can be designed using a peptide, antibody, nanoparticle, or other molecules [20]. Peptides are the most commonly described probes in molecular endoscopy as they offer certain advantages. They are small for mucosal penetration, are safe, have low immunogenicity, and are relatively easy and inexpensive to mass-produce. The peptide is isolated using a bacteriophage library and then labeled to a fluorophore to be applied topically during endoscopy using a spray catheter. Use of a multimodal video endoscope provides images using a special fluorescent and reflectance filter [21]. This technology has the potential for more accurate in vivo diagnosis and prediction of patients with higher risk of progression into neoplasia before morphologic changes even develop.

Endoscopic Evaluation of the Upper GI Tract

Barrett's Esophagus, Dysplasia, and Esophageal Adenocarcinoma

Rationale and Limitations of Surveillance Endoscopy

The global incidence of esophageal adenocarcinoma (EAC) is 0.7/100,000 person years and has significantly increased in Europe, Australia, and the United States in the last four decades [22, 23]. Most cases of EAC are diagnosed at advanced stages, which is associated with dismal survival and poor quality of life [24]. Barrett's esophagus (BE) or intestinal metaplasia (IM) of the esophagus is the precursor lesion for EAC and can be detected endoscopically in the presence of salmon-colored mucosa extending more than 1 cm proximal to the gastroesophageal junction with confirmed IM on biopsies [25].

Progression of BE to EAC involves a series of pathologic changes from non-dysplastic BE (NDBE) to low-grade dysplasia (LGD), high-grade dysplasia (HGD), and finally EAC [26]. Thus, endoscopic surveillance with targeted biopsies of visible lesions and four-quadrant random biopsies every 1–2 cm (Seattle biopsy protocol) is endorsed by international society guidelines to detect dysplasia or EAC at earlier stages, receive curative therapy, and enhance survival [25, 27–30]. Moreover, this approach can help identify patients with neoplastic lesions who are amenable to endoscopic eradication therapies (EETs) in lieu of surgery or chemoradiation. However, this approach has several limitations including sampling errors (focal distribution of neoplasia and surveillance biopsies sample only 5% of the Barrett's segment), limited reliability of histologic interpretation of dysplasia, and the associated costs, time, and labor, which may explain why community endoscopists do not adhere to the Seattle biopsy protocol [31, 32]. In addition, visible lesions can be easily missed because they are often small and focally distributed.

Endoscopic Inspection of BE

The endoscopist should inspect the Barrett's segment in a systematic fashion to maximize detection of visible lesions which can harbor dysplasia or early cancer. Careful evaluation of BE with HDWLE is recommended as the minimum standard to maximize detection of visible lesions [27, 33]. However, there are no randomized clinical trials directly comparing HDWLE with standard WLE for detection of visible lesions in BE, and this recommendation is inferred from several other studies [34, 35]. Longer inspection time, along with careful and organized BE inspection, may be associated with higher number of lesions detected and increased diagnosis of HGD/EAC [33]. Careful endoscopic examination can reassure detection of >80% of lesions with HGD/EAC [36].

The following recommendations can be considered to ensure high-quality care. First, consider the use of a transparent distal attachment cap on the tip of the endoscope to facilitate endoscopic view especially in patients with BE-related neoplasia. Second, clean the mucosa by using the water jet channel and carefully suctioning the fluid with minimal mucosal trauma. Third, inspect the suspected BE by varying insufflation

and desufflation to detect subtle surface irregularities. Fourth, inspect the distal Barrett's segment in a retrograde view. Fifth, describe the location of the diaphragmatic hiatus, gastroesophageal junction, and squamocolumnar junction, as well as the extent of BE including circumferential and maximal segment length using the Prague classification [37]. After adequate inspection of BE, biopsies can then be performed. Biopsies should be avoided in normal or irregular Z line to avoid overdiagnosis of BE in patients who in fact have IM of the cardia which is not associated with EAC and in areas of erosive esophagitis until optimizing antireflux therapy, as reparative changes from active esophagitis can be difficult to distinguish from dysplasia.

Uniform Evaluation of Visible Lesions

Subtle mucosal abnormalities, such as ulceration, erosion, plaque, nodule, stricture, or other luminal irregularities in the Barrett's segment, should be sampled separately, as there is an association of such lesions with underlying dysplasia and cancer [38]. These mucosal abnormalities should undergo endoscopic mucosal resection (EMR), as this provides a better sample for pathologic review and changes the histopathologic diagnosis in approximately 30–50% of patients, compared with biopsies [39, 40]. Moreover, EMR of suspicious esophageal lesions represents a quality indicator of EET of BE, both as a diagnostic (to determine the T-stage and/or grade of dysplasia) and therapeutic maneuver [35]. Chapter 3 of this book offers further details regarding esophageal EMR techniques.

The Paris classification provides a grading system for visible mucosal lesions, which facilitates uniform communication among clinicians [41]. Visible lesions are described as follows: protruded lesions, 0-Ip (pedunculated) or 0-Is (sessile); and flat lesions, 0-IIa (superficially elevated), 0-IIb (flat), 0-IIc (superficially depressed), and 0-III (excavated). Lesions classified as 0-Is, 0-IIc, and 0-III are most likely to harbor invasive cancer, whereas 0-IIa and 0-IIb are likely associated with early neoplasia (Fig. 1.2) [27]. The length of the lesion should be reported using the

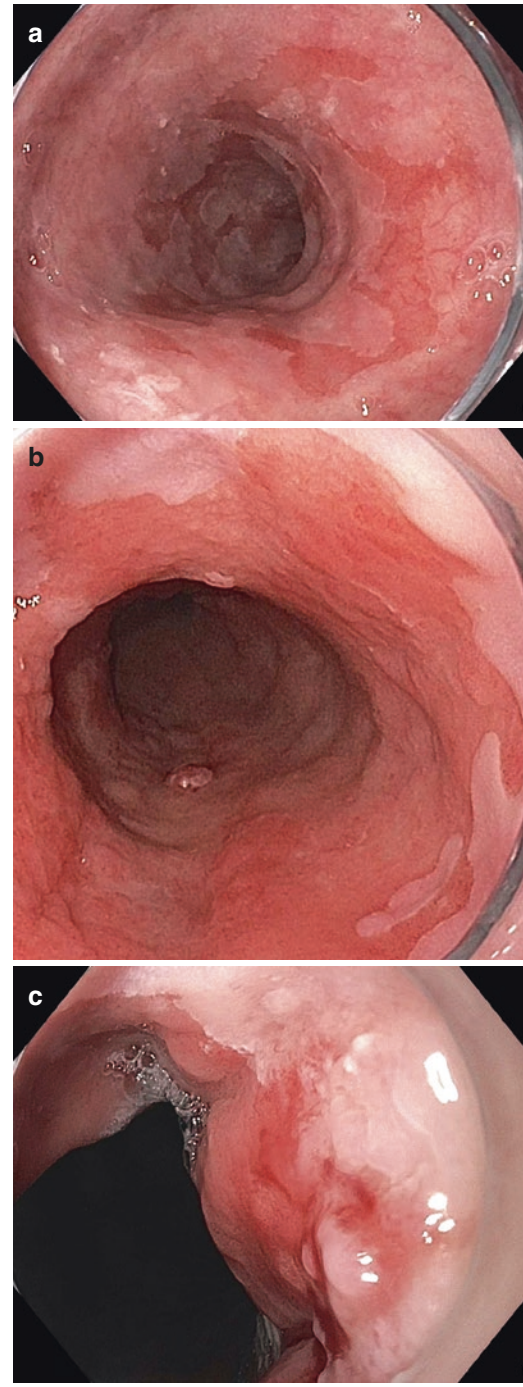

Fig. 1.2 Description of visible lesions in Barrett's esophagus using the Paris classification. (**a**) Flat Barrett's esophagus without visible lesions. (**b**) Paris IIa diffuse nodularity within Barrett's segment. (**c**) Paris IIa and IIc lesion within Barrett's segment

Table 1.2 Quality indicators for endoscopic eradication therapy (EET) in Barrett's esophagus (BE) and suggested median threshold benchmark

Type	Metric	Threshold
Pre-procedure	The rate at which the reading is made by a GI pathologist or confirmed by a second pathologist before EET is begun for patients in whom a diagnosis of dysplasia has been made	90%
	Centers in which EET is performed should have available HDWLE and expertise in mucosal ablation and EMR techniques	NA
	The rate at which documentation of a discussion of the risks, benefits, and alternatives to EET is obtained from the patient prior to treatment	>98%
Intra-procedure	The rate at which landmarks and length of BE are documented (e.g., Prague grading system) in patients with BE before EET	90%
	The rate at which the presence or absence of visible lesions is reported in patients with BE referred for EET	90%
	The rate at which the BE segment is inspected by using HDWLE	95%
	The rate at which complete endoscopic resection (en bloc resection or piecemeal) is performed in patients with BE with visible lesions	90%
	The rate at which a defined interval for subsequent EET is documented for patients undergoing EET who have not yet achieved complete eradication of intestinal metaplasia	90%
	The rate at which complete eradication of dysplasia is achieved by 18 months in patients with BE-related dysplasia or intramucosal cancer referred for EET	80%
	The rate at which complete eradication of intestinal metaplasia is achieved by 18 months in patients with BE-related dysplasia and intramucosal cancer referred for EET	70%
Post-procedure	The rate at which a recommendation is documented for endoscopic surveillance at a defined interval for patients who achieve complete eradication of intestinal metaplasia	90%
	The rate at which biopsies of any visible mucosal abnormalities are performed during endoscopic surveillance after EET	95%
	The rate at which an antireflux regimen is recommended after EET	90%
	The rate at which adverse events are being tracked and documented in individuals after EET	90%

proximal and distal margin of the lesion in relation to the endoscope distance from the incisors. The circumferential involvement should be reported using the lateral margins of the lesion relative to the clock position and with the endoscope in the neutral position.

Quality Indicators of Endoscopic Surveillance

Defining quality indicators may help to ensure the delivery of high-quality care. In this era of value-based and quality-based healthcare, the development of quality indicators that benchmark performance is critical. Thus, a recent study used a methodologically rigorous process to develop valid quality indicators for EET in the management of patients with BE-related neoplasia. The valid quality indicators were categorized into pre-procedure, intra-procedure, and post-procedure quality indicators. The performance threshold for each of these metrics can be found in Table 1.2.

Advanced Imaging Modalities (AIMs) to Enhance Surveillance

Several AIMs have been investigated to overcome some of the limitations of current surveillance practices of BE with WLE. A Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) statement from the American Society of Gastrointestinal Endoscopy (ASGE) has outlined thresholds for performing AIMs during endoscopic surveillance of BE [42]. To eliminate random biopsies, an AIM with target biopsies should have the following characteristics: (1) per-patient sensitivity of ≥90% and a negative predictive value of ≥98% for detecting HGD/EAC, compared with the

current standard protocol, and (2) specificity of ≥80% to allow a reduction in the number of biopsies compared with biopsies obtained using the Seattle protocol. A recent meta-analysis demonstrated that only experts in the field of BE meet these thresholds with acetic acid chromoendoscopy, NBI, and eCLE [43]. Thus, AIMs should not yet replace surveillance endoscopy with random biopsies in non-expert hands. However, AIMs can increase the diagnostic yield for identification of HGD/EAC if added to the Seattle protocol, as recently demonstrated in a meta-analysis with 34% and 35% incremental yield of HGD/EAC with virtual and conventional chromoendoscopy, respectively [44]. In head-to-head studies, both chromoendoscopy modalities have demonstrated comparable detection of HGD/EAC [34, 45].

Virtual Chromoendoscopy

The majority of studies evaluating virtual chromoendoscopy in BE have used NBI. In the largest international crossover RCT to date comparing NBI with HDWLE, there was significantly higher detection of dysplasia (30 vs. 21%) with NBI [46]. Several classification patterns (Kansas [47], Amsterdam [48], Nottingham [49]) have been proposed to predict histopathology based on NBI surface patterns, but the proposed criteria are complex, and validation studies had disappointing results. An international working group recently developed a simple and internally validated system to identify dysplasia and EAC in patients with BE based on NBI results [50]. This system, known as the BING criteria, can classify BE with >90% accuracy and a high inter-observer agreement. Regular mucosal patterns were defined as circular, ridged/villous, or tubular patterns; and irregular mucosa was marked by absent or irregular surface patterns. Regular vascular patterns were defined by blood vessels situated regularly along or between mucosal ridges and/or those showing normal, long, branching patterns; irregular vascular patterns were marked by focally or diffusely distributed vessels not following the normal architecture of the mucosa (Fig. 1.3). Additional studies are needed with BLI, FICE, and iScan to assess their utility and interpretation.

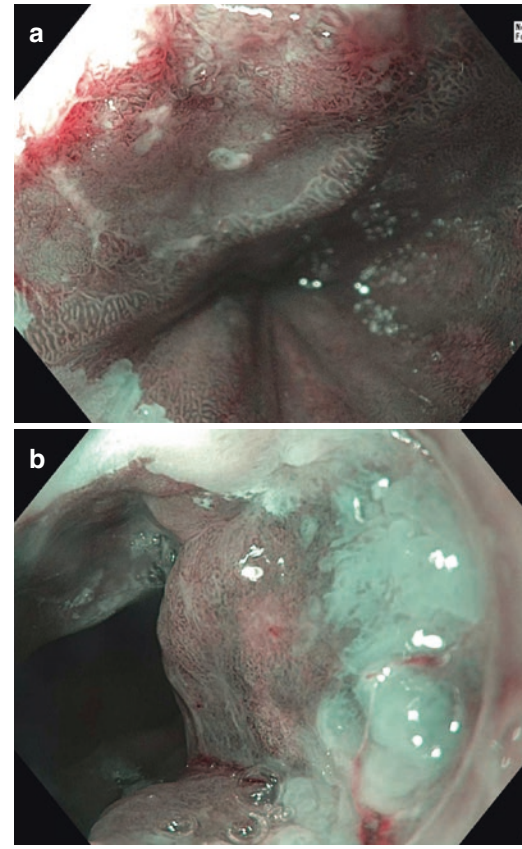

Fig. 1.3 Abnormal NBI pattern of visible lesions in Barrett's esophagus. (**a**) Paris IIa and IIc lesion with abnormal NBI pattern from 9 to 1 o'clock position and with normal NBI pattern from 1 to 9 o'clock position. (**b**) Paris Is lesion in the GE junction with abnormal NBI pattern

Conventional Chromoendoscopy

The dyes most commonly used for conventional chromoendoscopy in BE are acetic acid and methylene blue. No standardized classification criteria have been established for any dye. In the meta-analysis by Thosani et al., acetic acid chromoendoscopy was found to meet the thresholds established by the ASGE PIVI (sensitivity, 97%; negative predictive value, 98%; and specificity, 85%) and can be used in clinical practice at least by experts [43]. In contrast, methylene blue chromoendoscopy fails to meet these thresholds (sensitivity, 64%; negative predictive value, 70%; and specificity, 96%) and does not increase the diagnostic yield over random biopsies for the detec-

tion of HGD/cancer [43, 51]. Furthermore, the safety of methylene blue has been questioned as one study suggested that it can cause induce oxidative damage to DNA when photosensitized with light [52]. Acetic acid causes disruption of the columnar mucosal barrier in minutes, leading to whitening of the tissue with vascular congestion and accentuation of the villi and mucosal pattern when the acid reaches the stroma. The whitening effect in dysplastic areas is lost earlier than in the surrounding mucosa, which helps identify neoplastic areas.

Role of AFI, CLE, VLE, and OCT

Other AIMs have been investigated, but none appear to be ready for clinical application at the present time [53]. AFI is limited by its high false positive rate, fair to moderate inter-observer agreement, and minimal incremental diagnostic yield over the Seattle protocol [54]. CLE has the potential to confirm a real-time diagnosis of neoplasia without the need for histology, which could lead to immediate endoscopic therapy without biopsies, such as same-session EMR or ablative therapy. Use of eCLE meets the ASGE PIVI thresholds but is no longer commercially available, while pCLE does not meet these thresholds [43]. A meta-analysis recently showed that VLE is associated with a marginal increase in detection of HGD/cancer and has very high rates of false positive results [55]. However, OCT and VLE can evaluate epithelial thickness and buried glands, which can predict prolonged or failed ablation, and be useful in post-endoscopic ablation surveillance [56, 57]. The clinical applicability of these AIMs needs to be better defined before recommending their routine use in surveillance of BE.

Gastric Intestinal Metaplasia, Dysplasia, and Cancer

Rationale of Screening and Surveillance

Gastric cancer (GC) is one of the most frequent and lethal malignancies worldwide. The introduction of universal screening in Korea and Japan is associated with earlier GC diagnosis and lower cancer-related mortality [58–60]. Thus, universal screening is warranted in individuals from high-incidence countries, but is more selective in low-incidence countries based on demographic data and *Helicobacter pylori* status [61]. This translates in higher rates of early GC diagnosis – lesion confined to the mucosa or submucosa – in countries with national screening programs compared to Western countries (60 vs. 20%), which can be safely treated by mucosal or submucosal endoscopic resection [62, 63].

Compared with noninvasive tests, endoscopy is the best and most cost-effective screening modality to detect precancerous lesions and GC [64]. The development of intestinal-type GC is preceded by a cascade of several precancerous events that range from non-atrophic gastritis, multifocal atrophic gastritis (AG), IM, dysplasia, and ultimately GC [65]. Management and surveillance intervals are determined based on the individual histologic risk of progression into GC. A population study from the Netherlands illustrated this by showing an annual incidence of GC of 0.2% for AG, 0.3% for IM, 0.6% for mild-moderate dysplasia, and 6% for severe dysplasia [66]. The risk of GC with AG and IM can then be further stratified based upon location, severity, and extension of the lesion. Patients with widespread atrophy or IM pose high risk of cancer and require endoscopic surveillance every 3 years. Patients with LGD should be followed every 12 months, while those with HGD should be followed every 6 months or have the lesion resected [67].

Endoscopic Evaluation of Stomach Lesions

Endoscopic findings suggestive of superficial lesions such as light changes in color (redness or pale faded), irregularities of mucosal folds, absence of submucosal vessel pattern, and spontaneous bleeding should be carefully examined (Fig. 1.4a) [68]. Well-demarcated border or irregularity in color/surface pattern is more suggestive of malignant lesions. However, the sensitivity of WLE for identifying GC is ~80% and can miss

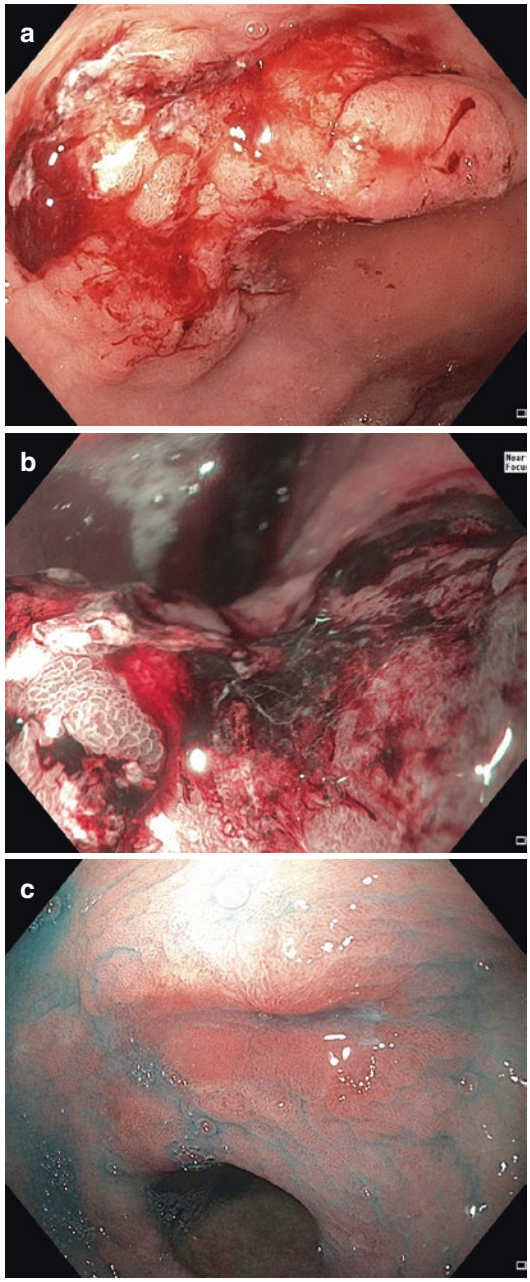

Fig. 1.4 Representative endoscopic images of gastric neoplasia. (**a**) Paris Is and IIc friable gastric mass. (**b**) Ulcerated gastric mass with abnormal NBI pattern. (**c**) Chromoendoscopy with methylene blue determining outer margins of early gastric cancer that was ultimately resected

small or flat lesions [68]. If endoscopic examination is normal, at least five nontargeted biopsies should be obtained according to the Sydney system in the antrum (×2), incisura angularis (×1), and body (×2) [69]. Biopsy specimens should be submitted in separate jars labeled by region of the stomach sampled. This protocol is sensitive for detection of atrophic gastritis and intestinal metaplasia when performed in high-risk populations [70].

Role of Virtual and Conventional Chromoendoscopy

After recognition of suspicious lesions with WLE, virtual and conventional chromoendoscopy help in lesion characterization and highlight lesion outer margins (Fig. 1.4b, c). Diagnostic accuracy of NBI is maximized with magnifying endoscopy, by analyzing the microvascular and microsurface patterns separately. In a recent meta-analysis of 14 studies, magnifying NBI showed high sensitivity (86%) and specificity (96%) for detection of early GC [71]. This showed to be especially helpful for depressed or small lesions ≤10 mm in size, which can be more accurate than with conventional chromoendoscopy [71, 72]. Magnifying NBI can also delineate the lateral margins of a lesion even when conventional chromoendoscopy is not able to determine the margins [73]. Further research is needed to establish a standard NBI classification system to reduce various biases and improve its diagnostic accuracy in the assessment of gastric lesions. For example, fine network patterns with abundant microvessels connected one to another are characteristic of adenocarcinoma, and a corkscrew pattern with tortuous isolated microvessels is characteristic of poorly differentiated adenocarcinoma. Conventional chromoendoscopy with indigo carmine and acetic acid has been used in clinical practice for evaluation of gastric lesions, but delineation of margins is not superior to NBI.

Role of AFI and CLE

The role of other AIMs has not been fully established in the screening or surveillance of GC. AFI has limited clinical value due to its high false positive rate and low specificity. CLE has shown encouraging results for the in vivo diagnosis of premalignant lesions and early gastric cancer [74].

Duodenal Adenomas and Cancer

Rationale for Screening and Surveillance

Duodenal cancer is rare among all GI malignancies. For several years, it has been recognized that this malignancy arises from an adenoma-to-carcinoma pathway similar to colorectal cancer (CRC) [75]. Duodenal adenomas should be categorized as being ampullary or non-ampullary and as sporadic or arising in the context of familial adenomatous polyposis (FAP). The lifetime risk of duodenal cancer in patients with FAP is 5–10%, while in the general population, it ranges from 0.01% to 0.04% [76]. In addition, duodenal adenomas are diagnosed in up to 90% of FAP patients, can be multiple, and involve the ampulla. Thus, endoscopic screening and surveillance are recommended in FAP patients [77].

Endoscopic Evaluation

Endoscopic evaluation should be performed using a distal attachment cap and often requires a duodenoscope to definitively determine lesion relationship to the major and minor papilla. Morphologic features including the size of the lesion, number of folds affected, percent of circumference involved, and Paris classification should be determined to decide on management (surveillance, endoscopic resection, or surgery) (Fig. 1.5a, b).

The Spigelman staging system is widely used to evaluate the severity of duodenal polyposis and consists of a five-grade scale (0 to IV) based on polyp burden (number, size, histologic type, and degree of dysplasia) [78]. The 10-year risk of cancer can be as high as 36% for Spigelman stage IV disease, but much lower (≤2%) for lower stages [79]. Thus, endoscopic staging helps to determine the surveillance and treatment strategies for FAP patients with duodenal adenomas [77].

Diagnosis of adenoma with HDWLE and forceps biopsies is highly sensitive (>90%), but the sensitivity for detection of adenocarcinoma is lower, and biopsies can miss up to 30% of ampullary cancers [80, 81]. Cancer should be suspected in the presence of irregular margins, ulceration, friability, or induration. Polyps larger than 1 cm have also been associated with advanced histology.

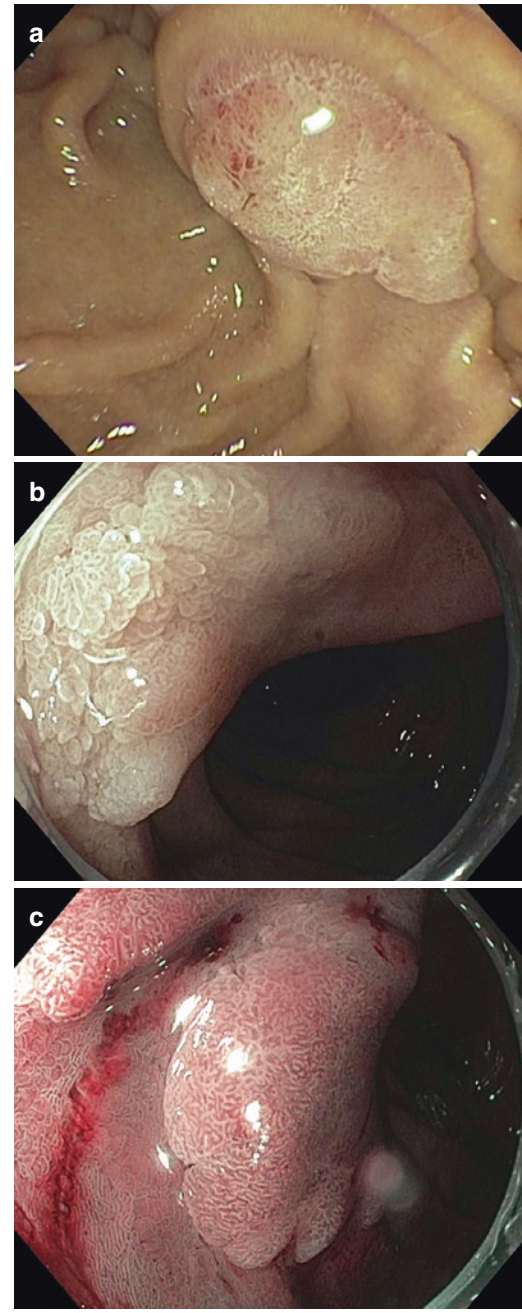

Fig. 1.5 Duodenal lesions. (**a**) Ampullary adenoma examined with duodenoscope. (**b**) Large duodenal adenoma in the second portion of the duodenum using forward view endoscope and a distal attachment cap. (**c**) Representative image of duodenal adenoma using NBI

Role of Advanced Imaging Modalities

NBI is helpful for detection of duodenal adenomas. Predictive features of adenoma include the presence of dense white villi, large duodenal villi, leaf-shaped villi, or irregular vascular pattern (Fig. 1.5c) [81, 82]. Conventional chromoendoscopy has not been well studied for duodenal adenomas, but could be used if NBI or virtual chromoendoscopy is not available [83]. Two studies have demonstrated that real-time readings provided with pCLE have a high degree of diagnostic value when histology is used as the gold standard and may have higher sensitivity than NBI [83, 84]. Endoscopic ultrasound and endoscopic retrograde cholangiopancreatography can assess if ampullary adenomas have intraductal extension, which could preclude ampullectomy.

Recognition of Lesions in the Lower GI Tract

Colon Polyps and Colorectal Cancer

Rationale for Screening and Surveillance of Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer in men and women [85]. Colon polyps are the precursor lesion and progress to cancer via the adenoma-carcinoma sequence (adenoma) or the serrated pathway (sessile serrated adenoma (SSA) or traditional serrated adenoma) [86]. With the implementation of CRC screening programs and polypectomy, the incidence and mortality of CRC have declined [87–90]. Therefore, endoscopic detection, diagnosis, and adequate resection of polyps are critical steps for prevention of CRC. Colonoscopy techniques to improve adenoma detection rates go beyond the aims of this chapter, but use of virtual or conventional chromoendoscopy does not seem to reduce missed polyp rates compared with WLE [91, 92].

Histologic Prediction of Polyps During Colonoscopy

After a polyp is found during colonoscopy, careful evaluation and classification can help histologic prediction. Diminutive polyps (≤5 mm) represent 70–80% of all resected polyps, approximately 50% are adenomas, and rarely harbor advanced histology such as villous features and HGD (1.1–3.4%) or cancer (0–0.08%) [93–95]. If diminutive polyp histology can be determined optically in real time without the expense of pathologic examination, significant cost reduction can be achieved without compromising clinical decision-making or quality.

Optical histologic diagnosis of diminutive polyps has led to the proposal of a "resect and discard" strategy for diminutive polyps determined to be adenomatous and a "do not resect" strategy if characterized as non-adenomatous. An ASGE PIVI statement has proposed thresholds that are needed to be met to follow these strategies: (1) For diminutive rectosigmoid non-adenomatous polyps to not be removed, the negative predictive value for adenoma should be greater than 90%. (2) For any type of diminutive polyps to be resected and discarded, there should be correct predication of surveillance interval accuracy greater than 90% [96].

Role of Advanced Imaging Modalities for Histologic Prediction of Colonic Lesions

Optical diagnosis cannot be achieved by the sole use of HDWLE. Adenomas have reddish appearance, while hyperplastic polyps are whiter. Sessile serrated adenomas (SSAs) are often flat, larger in size, covered by a mucus cap, and surrounded by a rim of debris, display a lacy vessel pattern, and have indistinct borders. There is strong evidence that discrimination between adenomatous and serrated polyps can be improved with conventional or virtual chromoendoscopy [97]. NBI has been extensively studied, and in expert hands it can meet the thresholds proposed by the ASGE PIVI statement [97, 98]. NBI-assisted optical diagnosis by non-experts has shown equivocal results in comparison to the PIVI thresholds and cannot currently be recommended for routine use outside of expert centers [95, 99]. Other virtual chromoendoscopy technologies such as iScan and FICE have also shown high reliability for optical diagnosis

[100]. Diagnostic accuracy with CLE appears to be as good as with NBI, but unsatisfactory with AFI [100].

Several classification systems have been developed for the assessment of colon polyps with NBI and chromoendoscopy (Table 1.3 and Fig. 1.6). The Kudo classification was the first to be developed and helps making in vivo histologic diagnosis of polyps based on surface pit pattern [101]. Pit patterns can be grouped into three basic types: (1) Kudo I and II have round/stellar pits and represent non-neoplastic lesions; (2) Kudo IIIs, IIIL, IV, and selected cases of Vi correspond to adenomas and cancers with superficial submucosal invasion (SMI) that are endoscopically treatable; and (3) Kudo Vn and some Vi harbor cancer with SMI and are not amenable for endoscopic resection. The NBI International Colorectal Endoscopic (NICE) classification gives a simplified and standardized system for optical diagnosis of polyps based on lesion color, surface pit pattern, and vascular pattern [102]. NICE type I is found with hyperplastic polyps and SSAs, type II in adenomas, and type III in CRC with SMI. In the most recent Workgroup serrAted polypS and Polyposis (WASP) classification system, an additional category is created to differentiate hyperplastic polyps and SSAs, due to the higher malignant potential for SSAs [103].

Endoscopic Prediction of Invasive Cancer and Determination of Resectability

Because of the unique absence of lymphatics in the colonic mucosa, CRC is defined as invasion of dysplastic cells in the submucosa (SMI), and lesions confined to the mucosa are better named LGD or HGD instead of "carcinoma in situ" or "intramucosal adenocarcinoma" [104]. Endoscopic resection is adequate for lesions with LGD or HGD, but lesions with SMI are associated with 1–16% risk of lymphovascular invasion (LVI), and further stratification is needed to determine if endoscopic

Table 1.3 Kudo, NICE, and WASP classification of colon polyps

Histology	Kudo pit pattern	NICE[a]	WASP[b]
Normal	**Type I** Round		
Hyperplastic	**Type II** Star-like, papillary	**Type I** *Color* Same or lighter relative to background *Vessels* None or isolated lacy vessels coursing across lesion *Surface pattern* Dark or white spots of uniform size or homogenous absence of pattern	**Sessile serrated adenoma** *If >2 features*: 1. Cloud-like surface 2. Indistinct borders 3. Irregular shape 4. Dark spots inside crypts
Adenoma	**Type III** Tubular/ roundish IIIS small IIIL large **Type IV** Gyrus-like, branched	**Type II** *Color* Browner than background *Vessels* Brown vessels surrounding white structures *Surface pattern* Oval, tubular, or branched white structures surrounded by brown vessels	
Deep submucosal invasive cancer	**Type V** Vi irregular Vn non-structural	**Type III** *Color* Brown to dark brown relative to background *Vessels* Areas with distorted or missing vessels *Surface pattern* Amorphous or absent surface pattern	

[a]NICE – NBI International Colorectal Endoscopic classification system
[b]WASP – Workgroup serrAted polypS and Polyposis

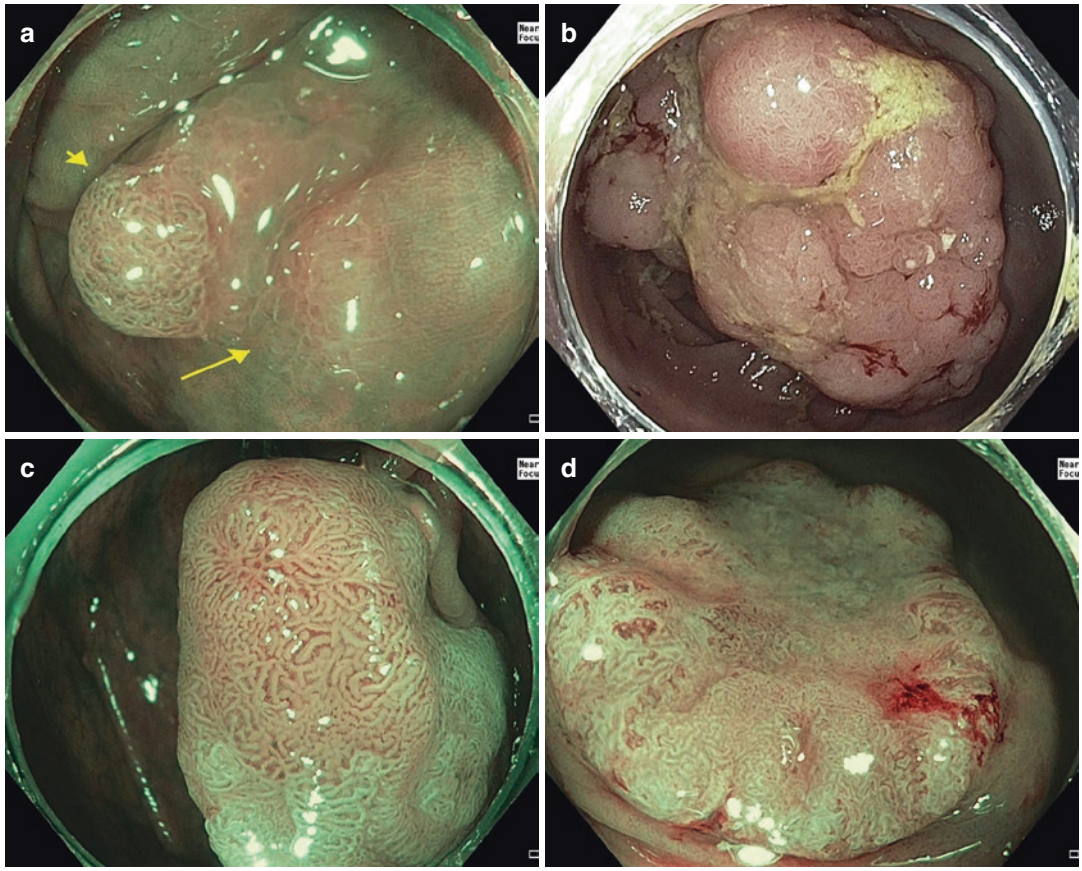

Fig. 1.6 Histologic prediction of different colon types. (**a**) Paris Is and IIb polyp, with Kudo II and IV pattern consistent with simultaneous serrated and tubulovillous histology. (**b**) Laterally spreading tumor with Kudo IIIs pattern consistent with tubular adenoma. (**c**) Kudo IV pattern consistent with tubulovillous histology. (**d**) Paris Is-IIc laterally spreading non granular tumor, with Kudo V and NICE III pattern. These features predicted submucosal invasion and endoscopic unresectability

resection is the adequate therapy [105]. Lesions with low-risk features such as superficial SMI (depth < 1 mm), well-differentiated tumor grade, and absence of LVI can be adequately treated endoscopically.

Real-time endoscopic prediction of SMI risk is essential before endoscopic resection is attempted [106]. The Paris classification of superficial neoplasia should be used for morphologic classification. Flat or sessile lesions larger than 10 mm can be designated as laterally spreading lesions (LSL) and can then be further categorized based on their surface topography into granular (G), nongranular (NG), or mixed morphologies. Focal interrogation of the pit pattern and vascular patterns with virtual or conventional chromoendoscopy is critical to further assess their risk of deep SMI. Factors associated with SMI include Kudo pit pattern V, NICE III pattern, a depressed component (0-IIc), rectosigmoid location, 0-Is or 0-IIa + Is Paris classification, nongranular surface morphology, and increasing size [107, 108]. The "non-lifting sign" is also associated with SMI but can also be found in submucosal fibrosis from prior biopsies or polypectomy attempts [109].

Colorectal Dysplasia and Cancer in Inflammatory Bowel Disease

Rationale for Dysplasia Surveillance

Patients with inflammatory bowel disease (IBD) have twofold higher risk of developing CRC compared with the general population [110].

Chronic inflammation, free radicals, and cytokines lead to genetic alterations and eventually dysplasia, which can then transition to CRC in IBD patients [111]. Thus, clinical practice guidelines recommended dysplasia surveillance to prevent CRC in patients with left-sided or extensive ulcerative colitis (UC) and for colonic Crohn's disease (CD) [112]. The efficacy of this approach has not been studied in clinical trials, but several population and observational studies have demonstrated reduction in cancer development and death associated with CRC in patients undergoing endoscopic surveillance [113–115].

Endoscopic Surveillance with High-Definition Endoscopy

Detection of dysplasia in IBD patients traditionally relied on WLE and extensive random biopsies (four every 10 cm) to identify invisible dysplasia [112]. The principle for this strategy was that dysplasia was often not accompanied by visible mucosal abnormalities during the fiberoptic endoscopy era. However, this has been increasingly disputed, and a systematic review revealed that in IBD patients with dysplasia, 80% are visible with standard WLE and 90% are visible with HDWLE or chromoendoscopy [116]. In addition, random biopsies are time consuming, distracting, expensive, and low yield – 1 episode of dysplasia detected for every 1505 random biopsies [117]. For these reasons, a targeted biopsy strategy has been developed and has been found to be superior to random biopsies for detection of neoplasia [118]. Despite these data, random biopsies have not yet been abandoned, and future studies should evaluate the incremental yield to targeted biopsies for dysplasia detection.

Recently, an international multidisciplinary group of 21 experts developed a consensus document aimed to optimize strategies for detection of dysplasia in IBD patients [116]. One of the key recommendations of this paramount document is to perform HDWLE instead of standard WLE for dysplasia surveillance of IBD patients. This is based on results from a retrospective observational study that found dysplasia to be found twice in patients undergoing HDWLE compared with those having standard WLE [3].

Uniform Terminology of Dysplasia

The SCENIC consensus also proposes that the terms dysplasia-associated lesion or mass (DALM) and adenoma-like lesion or mass (ALM) should no longer be used, and instead dysplasia should be described as visible or invisible. Visible lesions can be described using the Paris classification. Lesion margins should also be carefully examined. Dysplasia identified on random biopsies without a visible lesion should be defined as invisible dysplasia. Polypoid dysplastic lesions that occur proximal to areas affected by inflammation can be assumed to be sporadic adenomas.

Conventional Chromoendoscopy for IBD Surveillance

Another key recommendation of the SCENIC consensus is to use conventional chromoendoscopy rather than standard-definition WLE for surveillance of IBD patients [116]. A recent systematic review of randomized controlled trials recently confirmed this statement and showed that conventional chromoendoscopy identifies more patients with dysplasia compared to standard WLE [119]. This meta-analysis also showed that conventional chromoendoscopy was not superior to HDWLE or NBI. This has also been suggested in a recent randomized controlled trial, which showed that HDWLE and virtual chromoendoscopy in expert hands are not inferior to conventional chromoendoscopy for detection of dysplasia or cancer [120]. A large "real-life" retrospective cohort also recently showed that implementation of conventional chromoendoscopy in clinical practice does not increase dysplasia detection compared with WLE with targeted and random biopsies [121]. Thus, there is still debate whether conventional chromoendoscopy should be adopted in all surveillance colonoscopies for IBD patients as it adds time and costs, and requires additional endoscopic training.

When conventional chromoendoscopy is used, visible lesions should be categorized using the crypt architecture with the Kudo pit pattern classification (Fig. 1.7). The two main stains are indigo carmine and methylene blue. Pancolonic rather than local staining is recommended, using

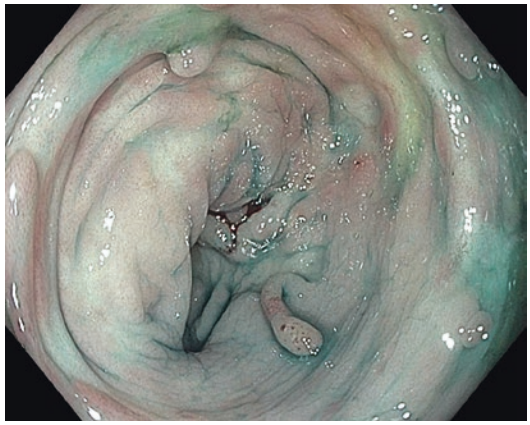

Fig. 1.7 Chromoendoscopy in IBD. Chromoendoscopy with methylene blue in a patient with well-controlled pan-ulcerative colitis, showing pseudopolyposis with Kudo I pattern

a spasmolytic if needed during withdrawal, excluding patients with active disease or inadequate bowel preparation. Pancolonic staining involves circumferential application of 250 mL of diluted dye (indigo carmine 0.3–0.1% or methylene blue 0.4–0.1%) throughout the colon after cecal intubation, using the water pump irrigation system or a spray catheter. Once a suspicious lesion is identified, approximately 30 mL of a more concentrated dye (indigo carmine 0.13% or methylene blue 0.2%) should be sprayed directly from a 60 mL syringe through the biopsy channel [116].

Virtual Chromoendoscopy and Other Technologies

NBI has not been shown to improve dysplasia detection compared with standard WLE, HDWLE, or conventional chromoendoscopy and is not recommended for surveillance of IBD patients [116]. Current endomicroscopic tools allow precise prediction of neoplasia on IBD by obtaining optical biopsies in real time, but several barriers limit their routine use in clinical practice [122]. The use of full-spectrum endoscopy (FUSE), a novel technology that incorporates two additional lateral cameras for 330° panoramic views, and stool DNA analysis, appear as promising tools for dysplasia detection in IBD patients but are not yet ready for clinical use [123, 124].

Training in AIMS

Medical societies have started to move away from a fixed time-based training to a system of competency-based education. This is structured on different assumptions: (1) people learn in different ways; (2) learners achieve competency at different rates; and (3) competency must be assessed against a fixed criterion rather than comparison against the performance of other learners or experts. Competency-based education of AIMs should be incorporated in gastroenterology fellowship training and needs development for those gastroenterologists already in practice. Training in AIMs can be obtained through classroom training programs or self-directed computer-based training modules [125]. A large body of evidence suggests that the use of these training methods in ex vivo and in vivo performance can lead trainees and academic or community endoscopists to meet the thresholds set forth by the ASGE for characterizing colon polyps with NBI examination [95, 126, 127]. These training methods are only moderately accurate among trainees for detecting neoplasia in BE with NBI [128]. Data for other AIMs is very limited to absent [129]. Future studies should assess training methods and learning curves needed to reach competency of individual AIMs in neoplasia detection and lesion characterization in the esophagus, stomach, duodenum, and colon. In the meantime, these training methods, in addition to image/video atlases, endoscopy simulators, and skill maintenance programs, should be used for motivated endoscopists.

Future Directions and Conclusions

The field of gastrointestinal endoscopy has evolved since the introduction of video endoscopy 25 years ago, with development of several advanced imaging modalities and other technologies that allow better lesion recognition and characterization. Future studies should focus on cost-effectiveness, training, and competency in the use of AIMs. The role of newer technologies such as autofluorescence, CLE, OCT, and VLE

still needs to be better determined before adoption in clinical practice. In the near future, molecular imaging may allow for more accurate in vivo diagnosis and prediction of patients with higher risk of progression into neoplasia before morphologic changes develop.

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